

Controlled Release Strategies for Pulmonary Delivery of Proteins/Peptides

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Abstract

Delivery of proteins via the pulmonary route for systemic activity has attracted considerable attention over the last decade. However, the issue of short duration of action of drugs delivered through this route has continued to challenge drug formulators and various strategies have been developed. This paper reviews possible controlled release strategies for inhaled proteins/peptides.

Introduction

The formulation and delivery of therapeutic proteins for systemic activity continues to challenge development scientists. Protein molecules are required to maintain higher order (2°, 3° and in some cases 4°) structures which are often easily disrupted. In addition protein molecules are vulnerable to gastro intestinal enzymes and extremes of pH that are present in the GI tract and once absorbed are often removed to a high degree by hepatic metabolism. For these reasons it is easy to understand the challenges with developing protein formulations for oral administration.

Other routes of administration have been investigated, however to date there has been little success or market penetration for delivery systems other than injectable systems. The exception to this seems to be the inhalation route which offers huge potential for the delivery of proteins.

The inhalation route offers several advantages over other routes of administration:

- Large absorptive surface area
- Thin diffusion pathway to the blood stream
- Elevated blood flow
- Avoidance of first pass metabolism
- Generally well accepted route of administration

These advantages mean that protein molecules can be readily absorbed and enter the systemic blood stream quickly with a high bioavailability compared to other routes of administration. However the rapid absorption of proteins via the inhalation route can lead to a short duration of action (Cefalu et al., 1998) and may require patients to take multiple daily doses. There is therefore a benefit in the development of controlled/sustained release methods for pulmonary delivery of proteins to increase patient compliance with medications. This paper summarises the key strategies that have been discussed in the literature to date for the controlled release of proteins/peptides.

The three key strategies are:

- Use of polymeric materials
- Microcrystallisation
- Liposomes

Encapsulation or entrapment of proteins in bio-compatible polymeric devices represents the most widely reported systems for the controlled release of peptides and proteins. Polymers such as PLGA, PLA, PEG and chitosan have been applied as delivery vehicles in pulmonary delivery of proteins, producing sustained systemic therapeutic activities. Proteins such as Insulin and deslorelin have either been conjugated to PEG or encapsulated in PLGA, PLA or chitosan for controlled release activity via the pulmonary route (Leach et al., 2003).

Insulin-PEG.

PEG has successfully been conjugated to insulin with a resultant controlled release profile following endotracheal tube delivery into the lungs of beagle dogs (Leach et al., 2003).

PEG-Insulin inhalation maintained glucose suppression for 6 to 12 hours as compared to 3 to 4 hours of glucose suppression for unmodified insulin.

Insulin-PLGA.

Insulin has been encapsulated in PLGA by emulsion solvent evaporation forming particles of mean diameter of 400nm. Following the administration of these nanospheres into the trachea of a fasted guinea pig, the blood glucose level was reduced significantly and the hypoglycaemia was prolonged for 48 hrs compared to the nebulized aqueous solution of insulin as a reference (6 hrs) (Kawashina et al., 1999) Deslorelin, a leutinizing hormone regulatory hormone agonist which is being studied for the treatment of cancer in humans and used for the induction and timing of ovulation in mares has also been encapsulated in PLGA (Koushik and Kompella, 2004), producing a 7 day in vivo drug release.

Microcrystallization

The use of protein microcrystal has been discussed as a potential means for controlled release delivery of therapeutic proteins. This process is advantageous over the other strategies discussed in that the process does not rely on additional components to the formulation and hence is a more simplistic system. Kwon et al. (2004) have described a process for the preparation of Insulin microcrystal with a mean volume diameter of 3µm. The process used in this example was seed zone crystallisation which gave yields in the region of 96%. The microcrystals obtained were rhombohedral with some rhombus forms. Diabetic rats administered with intratracheal instillation of the microcrystalline suspension had a longer time to minimum blood glucose level and lower blood glucose levels up to 13 hours after administration compared to rats administered with an insulin solution. In addition the intratracheal inhalation of microcrystalline suspension had an increased Tmax of 5 hours compared with 2 hours for insulin solution. However the more significant difference can be observed where an i.p bolus of glucose was administered at 5 hours, the glucose levels for subjects administered with solution insulin increase to greater than 90% of initial levels compared with just 50% for rats treated with microcrystalline insulin.

Liposomes

The use of liposomes for the generation of controlled release particles suitable for delivery via the pulmonary route has also been widely reported in the literature. For example, Bennett et al. (1994) outline a study whereby the LHRH antagonist detirelix was incorporated into negatively charged liposomes composed of distearoyl-L-a-phosphatidylcholine, distearoyl-L-aphosphatidylglycerol and cholesterol. Their investigations concluded that liposomal formulations of detirelix gave rise to plasma concentrations being sustained for a period of 4 days following pulmonary delivery. In their recent paper, Huang et al. (2006) demonstrated successful and sustained reduction of blood glucose level following the administration of nebulised liposome encapsulated insulin to diabetic mice. Reduced blood glucose levels were observed to be significantly lower when comparing liposome encapsulated insulin to insulin and liposome administered separately.

Discussion/Conclusions

The strategies discussed in this paper have demonstrated the ability to control the release of protein molecules. In addition some techniques have also shown the ability to increase the stability of the protein under investigation (Thanoo et al., 1992). However loss of protein activity is still a primary concern when processing material for controlled release. Loss of activity has been observed in polymeric microspheres systems (Sanchez et al. 1999). A further consideration for the use of polymeric material is the potential for polymers to accumulate in the lung (Patton et al., 1999). Microcrystallisation may offer solutions to these challenges but it remains to be seen if all proteins are amenable to this process or if the resultant particles provide the necessary release profile.

References

- Bennett et al.**, 1994. Sustained delivery of detirelix after pulmonary administration of liposomal formulations. *J. Cont. Rel.* 32, 27-35.
- Cefalu et al.**, 1998. Treatment of type 2 diabetes mellitus with inhaled human insulin: a 3-month, multicenter trial [abstract]. *Diabetes* 47,A61.
- Huang et al.**, 2006. Pulmonary delivery of insulin by liposomal carriers. *J. Cont. Rel.* 113, 9-14.
- Kawashima et al.**, 1999. Pulmonary delivery of insulin with nebulized dlactide/ glucolide copolymer (PLGA) nanospheres to prolong hypoglycemic effect.
- Koushik and Kompella**, 2004. Preparation of large porous deslorelin-PLGA microparticles with reduced residual solvent and cellular uptake using supercritical CO2 process. *Pharm. Res.* 21, 524-535.
- Kwon et al.**, 2004. Insulin microcrystal suspension as a long acting formulation for pulmonary delivery. *Eur. J. Pharm. Sci.*, 22 107-116.
- Leach et al.**, 2003. Dry powder formulation of inhaled PEG-Insulin yields prolonged systemic activity in dogs. Presented at ADA 63rd scientific sessions.
- Patton et al.**, 1999. Inhaled insulin. *Adv. Drug Deliv. Rev.* 35, 235-247.
- Sanchez et al.**, 1999. Formulation strategies for the stabilization of tetanus toxoid in poly(lactide co-glycolide) microspheres. *Int. J. Pharm.* 185, 255-266